Pediatric Pharmacogenetics: Pursuing Translation through a Pediatric CERT

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Translation Research

Objective

The mission of the AHRQ-funded Centers for Education and Research on Therapeutics (CERTs) is to advance the optimal use of drugs, increase awareness of their benefits and risks, and improve quality at reduced cost.

One goal of the CERT at Cincinnati Children's is to help foster pharmacogenetic (PG) projects that meet this mission, specifically seeking projects that will help demonstrate 'real world' validity and impact.

Projects

Current PG projects within the CERT:

Project 1

Serious mental health disorders: Risperidone

Project 2

Renal transplant: Mycophenolate mofetil (MMF)

Project 3

ADHD: Methylphenidate

Serious mental health disorders: Risperidone

Background

- Risperidone, a commonly prescribed antipsychotic, is affected by CYP2D6 and 5-10% are poor metabolizers
- Little clinically relevant pediatric research on CYP2D6 PG impact on risperidone

Method

Feasibility study of risperidone pharmacogenetics (CYP2D6) seeking to recruit a phenotypically homogeneous sample from a clinical inpatient setting

3-18 yrs old, inpatient or outpatient, poor metabolizer, new risperidone start, no other CYP2D6 inhibiting meds

Results

The feasibility of risperidone PG trial embedded in actual clinical care was low: polypharmacy was common, prescribing patterns shifted rapidly, and logistics hindered enrollment

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Renal transplant: Mycophenolate mofetil (MMF)

Background

•MMF is used for immunosuppression in ~70% of children who receive kidney transplantations

•Body surface area based dosing leads to wide variation in exposure between subjects

•High frequency of leucopenia (25-35%) often causes empiric decreased dosing, leading to increased rejection risk

Method

Case-control study of the role of PG (6 genes, 16 SNP's) in mycophenolate mofetil (MMF)-related leukopenia in children who receive kidney transplantation using the Midwest Pediatric Nephrology Consortium

Results

9 of 10 clinical centers have completed IRB approval and are currently enrolling patients

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ADHD: Methylphenidate

Background

•Robust data show that psychostimulants are effective treatments for ADHD symptoms

•Due to substantial individual dose-response variability, stimulant dosing by trial-and-error

•22 ADHD pharmacogenetic trials in children, but findings not consistent and many limitations

Method

Placebo-controlled within subject crossover trial examining PG (6 genes) of methylphenidate dosing and side effects in children with ADHD aged 7-11 years

Results

Target population successfully enrolled, data collection and genotyping are complete, and analysis is underway

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Overall Conclusions

Several early conclusions emerge from our translational focus within a CERT center. PG must be optimized for actual clinical use, but the very complexity of that care makes embedding PG trials extremely challenging. Focusing on high prevalence phenotypes (ADHD) and/or on medications with few good alternatives (MMF) help address this challenge. Piggybacking on an NIH study (ADHD) and using a multi-center network (kidney transplantation) offer tremendous synergies.

Next likely steps include a focus on clinical variables that will modify PG's impact (e.g., adherence) and developing a study within a quality improvement practice network to ensure final results are reliably translated into care.

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